Utilizing multi-sonographic measures in the detection of clinically diagnosed carpal tunnel syndrome, compared to nerve conduction studies: A pilot study

Undergraduate Thesis

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Abstract

Carpal tunnel syndrome (CTS) has shown increasing incidence rates over the last few decades. This upward trend will likely continue, correlating with increases in contributing factors, including obesity, diabetes, increased age, and occupational strain. Carpal tunnel syndrome is generally diagnosed clinically but confirmed with nerve conduction studies (NCS). The use of NCS as the gold standard has been argued in the literature, largely based on false negative rates up to 34%. Additionally, the invasive and costly nature of NCS has prompted the exploration of alternative methods. Sonography has shown great promise, reporting comparable predictive values in current literature. Although sonography provides a cost-effective, well tolerated, non-invasive evaluation, clearly identified methods for diagnosing and categorizing the severity of CTS have not been established. The purpose of this pilot study was to determine if a blended approach using sonographic and clinical indicators could improve the predictive value and provide clinicians with a feasible alternative for diagnosing and categorizing the severity of CTS. A retrospective case-control study was conducted to identify the most sensitive variables and establish a severity classification method based on sonographic and clinical indicators. Symptomatic subjects and asymptomatic controls were compared, as were variables amongst NCS severity categories. Sonographic and clinical indicators associated with CTS included increased cross-sectional area (CSA), abnormal longitudinal appearance and restricted excursion of the median nerve, presence of classic and nocturnal symptoms, and positive provocative testing. Ultrasound severity categorization using a combination of these indicators matched 63% of NCS results, and 84% of asymptomatic controls were identified as normal using the scoring system. This pilot data is a useful step in isolating salient variables that could be further explored

in replicated studies with increased recruitment. Confirmatory studies may provide clinicians with a holistic approach for the initial diagnosis and categorization of CTS.

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Chapter 1: Introduction

Background

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy and the most common work-related musculoskeletal disorder. Although CTS is a known work-related injury, idiopathic and secondary CTS are also frequent diagnoses. Regardless of the etiology, the ensuing pathophysiology of the median nerve follows a similar path, resulting in CTS. Diagnoses may rely on clinical evaluations, electrodiagnostic studies (EDX), or sonographic examinations (US). The treatment of CTS varies according to severity, ranging from conservative treatments to surgical interventions.

Carpal tunnel syndrome spans the globe, with general population incidence rates of 3.76 per 1000 person-years in the United States to 4.96 per 1000 person-years in Korea, with incidence rates showing an increase over time.[1,2] Increased incidence rates have been observed in employed CTS patients as compared to unemployed CTS patients, and particular occupations are considered at risk for developing work-related musculoskeletal injuries.[3] Sonography is an example of an at-risk occupation due to the frequency, duration, and nature of the examinations. Studies have indicated approximately 65% of sonographers have experienced CTS symptoms during their career and over 90% have reported working in pain.[4-8] Although occupational factors such as repetitive strain, vibration, and malpositioning increase the risk of CTS, over 50% of CTS cases are idiopathic.[9] Secondary CTS may result from conditions and diseases including pregnancy, obesity, diabetes, thyroid disorders, rheumatoid arthritis, amyloidosis, trigger digit, and cervical radiculopathy. Space occupying lesions or masses located within the carpal tunnel may also cause secondary CTS.[10-12]

Repeated or endured compression and stress on the median nerve creates a cascade of pathological responses, resulting in carpal tunnel syndrome. Elevated pressure and stress cause impaired nerve perfusion, triggering ischemia and damage to the nerve-blood barrier within the endoneurial capillaries. Leakage from the microvessels into the endoneurium leads to increased pressure and edema. Edema initiates the inflammation process as fibroblasts infiltrate the region. The ensuing fibrosis results in scar tissue formation, axonal injury, and localized demyelination. Diffuse demyelination and Wallerian degeneration occur with prolonged stress.[10-14] Symptoms progress as the severity of the individual's CTS increases. Early symptoms include intermittent numbness, tingling, burning, or pain in the lateral palm, thumb, index and middle fingers. Nocturnal symptoms may also occur, causing affected individuals to awaken from pain and numbness. Symptoms progress to grip and digit awkwardness, constant numbness, and decreased pain due to sensory loss as CTS severity increases. At the advanced stage of CTS, the patient experiences muscle atrophy and increased weakness.[1,4,10,11]

Diagnosis of CTS often relies on a clinical diagnosis, confirmed by EDX testing. Sonographic examinations have also proved useful for the evaluation of CTS. Clinical diagnosis should include symptom specifics, such as location, characteristics, and provocative and mitigating factors, and may include the use of functional status surveys (FSS) and symptom severity surveys (SSS), such as the Boston Carpal Tunnel Questionnaire. Clinical diagnoses also utilize physical testing including Phalen's test, Reverse Phalen's test, Tinel sign, carpal tunnel compression test (with and without wrist flexion), and hand elevation test. Electrodiagnostic tests include electromyography (EMG) and nerve conduction studies (NCS). Of the two, NCS is the more commonly used EDX testing.[10] Although EDX, more specifically NCS, has historically been considered the gold standard for confirming CTS diagnosis, its use as the gold standard has

been debated within the research literature.[1,15-17] Radiologic imaging, including sonography, has also been incorporated as a diagnostic tool. Sonographic evaluations of CTS patients typically evaluate the cross-sectional areas (CSA) of the median nerve at the proximal carpal tunnel. Magnetic resonance imaging (MRI) and computed tomography (CT) has also been employed in the diagnosis of CTS.

Treatment of CTS also varies according to the severity of the pathology. Conservative treatment includes splinting, oral medications, and injections such as corticosteroids. In more advanced CTS, surgery may be necessary. Carpal tunnel surgery involves the division of the transverse carpal tunnel ligament to alleviate compression of the median nerve, and may be performed either openly or endoscopically. Open carpal tunnel release is the most common surgical method, and has shown high success rates.[10] Although surgery usually has a high success rate, some CTS patients may have persistent symptoms, requiring further evaluation.[9,10]

Significance of the Problem

Current trends in CTS risk factors will likely result in an increased prevalence of CTS. Diabetes, obesity, an increasing life span, and occupational risks are several of the contributing factors expected to increase the incidence rate.[1,3,10] Research has indicated a prevalence rate of diabetes and obesity twice as high in CTS patients than that found in the general population.[3] As these trends increase so too will the need for a reliable, non-invasive method of assessing and diagnosing CTS. Clinical diagnosis, including symptoms and physical tests, has been shown to have high predictive values, and has been utilized as the gold standard in several studies rather than NCS.[15,16,18] More commonly, a clinical diagnosis of CTS is followed by confirmatory EDX

studies. Electrodiagnostic studies are invasive, uncomfortable, time consuming, and costly. Additionally, the results of EDX studies are questionable, including high rates of false-positives and a wide range of sensitivities reported within the research.[2,9,15-17,19]

Sonography is widely available throughout the world and examinations are cost-efficient, portable, and well tolerated by patients. The non-invasive nature and lack of radiation makes sonography an ideal modality for repeat examinations. The sonographic evaluation of CTS is commonly used but sensitivity rates have not consistently exceeded those of NCS. Evaluation of the CSA of the median nerve has been reported as beneficial for sonographically assessing CTS.[9,10,12,15,18-24] It has been proposed that sonography may replace NCS as a first-line test to confirm clinically diagnosed CTS, potentially eliminating the need for NCS in over 50% of the patients.[15,18] Evaluating multiple variables, both sonographic and clinical CTS indicators, may provide a more inclusive assessment of physiologic changes in the median nerve and the most accurate representation of the patient's pathology.

Research Objective

An increase in sensitivity, specificity, and predictive value rates is necessary before implementing the wide-spread use of sonography as a first-line diagnostic tool for CTS. The current trend in sonographic investigation of CTS focuses primarily on median nerve CSA however a multivariate approach may add value to the sonographic examination. Because of the complex cascade of pathological effects observed in the development and advancement of CTS, multiple factors should be assessed. Specifically, the median nerve should be evaluated for an increased CSA, abnormal longitudinal appearance, restricted excursion, and intraneural

vascularity. By assessing multiple variables in addition to the CSA, sonographic evaluation efficacy may match the gold standard of diagnosis provided by NCS in the detection and evaluation of clinically diagnosed CTS.

Chapter 2: Literature Review

As mentioned previously, clinical diagnosis relies on patient history, specifically symptom characteristics, and physical testing (Phalen's, Reverse Phalen's, Tinel, carpal tunnel compression, hand elevation). It is not uncommon for research studies to refer to clinical diagnosis as the gold standard in lieu of NCS. A general population study in Korea, including 97% of the population, reported 80% of CTS patients did not undergo electrodiagnostic testing (EDX), with medical practitioners relying solely on clinical diagnosis.[2] The presence of multiple primary symptoms of CTS has been found to have a high predictive value.[15-18] Although some studies have indicated relatively low sensitivities and specificities for individual clinical tests,[25] an increase in their predictive value when combined with other clinical indications and testing has been reported, with sensitivity rates as high as 99%.[15-18]

Electrodiagnostic studies are often used to confirm clinically diagnosed CTS. Nerve conduction studies evaluate the function of the median nerve, measuring the sensory and motor latencies, amplitudes, and velocities of the median nerve. Because EDX requires needles to be inserted into the upper extremity, it is considered an invasive and uncomfortable procedure. Nerve conduction studies are also costly; with a reported cost twice that of a sonographic examination.[15] While it is often referred to as the gold standard in research, its added value for clinically diagnosed CTS has been questioned.[15] Nerve conduction studies have consistently reported higher sensitivity ratings than sonography, however false-positives and false-negatives, especially in asymptomatic patients or cases of mild CTS, plague the use of NCS.[15-17,24] False-positive rates ranging from 10-20% and false-negative rates of 16-34% in clinically diagnosed CTS patients have been reported. Similarly, it has been reported that less than 50% of asymptomatic patients had positive NCS findings.[16,24] Sonography has been proposed as an

alternative to NCS as a confirmatory tool for CTS, with hopes of a well-tolerated examination, reduced medical expenses, and a diagnostic findings equal to or greater than those of NCS.

The majority of sonographic evaluations have relied on the CSA of the median nerve to evaluate the presences of CTS, with increasing areas correlating to an increase in severity.[20,24] Edema is one aspect of compressive neuropathies, resulting in the swelling of the median nerve at the carpal tunnel inlet. The flexor retinaculum flattens the median nerve as it travels through the carpal tunnel. As the median nerve exits the carpal tunnel distally it again takes on a swollen appearance. The cross-sectional imaging of the median nerve allows the area to be calculated using either direct trace methods or anteroposterior and mediolateral diameters. Cross-sectional area has been found to correlate well with both patient-oriented parameters, such as the Boston Carpal Tunnel Questionnaire, and with NCS findings.[24] In a meta-analysis of 19 prospective studies (3131 wrists) comparing sonography to clinical and NCS diagnoses, Fowler et al.[15] reported sonography had a sensitivity and specificity of 77.6% and 86.8%, respectively, when evaluating CSA. Sensitivities ranged from 57-98% and specificities ranged from 63-100%. The authors concluded the accuracy of sonographic evaluation may improve with higher CSA cut-off values employed.

The location for imaging CSA varies within the research as does location definitions.[16,22] Cross-sectional areas have been imaged proximal to the carpal tunnel, at the carpal tunnel inlet, and distal to the carpal tunnel, as well as in the forearm. Common verbiage describing imaging locations include carpal tunnel inlet, proximal carpal tunnel, distal carpal tunnel, carpal tunnel outlet, and at the wrist crease (also using locators such as distal, mid, and proximal). The location is often identified by the carpal bones, such as the level of the pisiform, but this too varies within research.[16] The location may affect the significance of the findings. Rahmani et al.[19] determined

there were significant differences between CTS patients and controls when the CSA was acquired at the wrist but when imaged at the forearm there were no differences between the groups. Akcar et al.[21] found statistically significant differences between CTS and control groups when the CSA was acquired at "mid-level", located at the level of the pisiform, but the CSA acquired proximal to the carpal tunnel inlet was not found to be a "clinically important predictor". A systematic review conducted by Roll et al.[25] postulated the pisiform would identify the level of the mid-carpal tunnel because of the distal arching of the proximal row of carpal bones. Roll suggested using the distal radial-ulnar joint, pisiform, and hamate as the carpal tunnel inlet, mid-carpal tunnel, and outlet, respectively. The most accurate CSA measurements were at the level of the pisiform, followed by CSA measurements immediately proximal to the inlet. Measurements at the distal carpal tunnel had the lowest accuracy, with a sensitivity rate ranging from 18-65%.[25] Area differences between the CSA values proximal to and within the carpal tunnel has shown diagnostic accuracy in confirming CTS. Akcar evaluated the CSA area difference between the level of the pisiform (CSAb) and proximal to the carpal tunnel (CSAa). Using a cut-off value of 3.65, CSA area difference (CSAb-CSAa) reported 83% sensitivity and 82% specificity.[21]

Although the level at which the measurements are acquired has been debated, an increased CSA is considered a consistent criterion.[9,10,12] Padua et al. found a significantly strong positive relationship between increasing CSA values and the increasing severity of clinical impairment in CTS patients ($r=0.80$, $p<0.0000001$).[20] El Miedany et al.[24] also evaluated CSA values to propose a severity grading system based on a strong correlation between increasing CSA levels and EMG and clinical findings. The authors proposed a CSA of 10-13mm² as mild, 13-15mm² as moderate, and greater than 15mm² as severe.[24] Optimal cut-off points have varied,

ranging from 9mm² to 15mm² throughout the research.[6,9,12,15,16,18,21-24] Cross-section area has proven to be valuable in the assessment of CTS, however varying cut-off points have affected the comparison of sensitivity ratings.

Excursion is a measure of the distance traversed by the median nerve as it glides through the nerve bed during flexion and extension movements. As the nerve bed is elongated, stress and strain of the median nerve occur. Increased strain negatively impacts conduction and blood flow within the nerve, leading to nerve injury.[14,26] In addition to nerve bed elongation during movement, physiologic changes occurring in CTS may invoke an increased strain on the median nerve. [9,11,13,14,26] Inflammation of the median nerve impedes movement through the carpal tunnel. Collagen deposition and fibrosis may cause thickening of the connective tissue, impairing nerve gliding. Fibrosis and scarring can also cause adhesion of the median nerve to surrounding tissue, reducing excursion by a tethering effect.

Studies have indicated specific positions and movements evoke specific excursion reactions. Forearm supination results in a greater excursion than pronation,[27] extension results in a greater excursion than flexion, [27,28] and distal excursion results from extension rather than flexion.[26,27,29-31] Median nerve excursion measurements have varied in the research. Wright et al. observed a 9.2mm excursion upon wrist extension in cadavers.[26] Lower excursion rates in healthy individuals were demonstrated by the Dilley et al. and Echigo et al. in vivo studies, ranging from 2.6-6.0mm and 1.8-3.0mm upon wrist extension, respectively.[27,30,32] Two sonographic modes commonly used to evaluate longitudinal median nerve excursion are spectral Doppler and frame-by-frame cross-correlation analysis. Doppler imaging encompasses capturing the longitudinal excursion test movements and correlating Doppler waveforms. The extension phases of the test movements are traced, resulting in velocity time integrals (VTI) representing

the median nerve excursion. The VTI are calculated in pixels and then converted into millimeters using programs such as Excel.[28,33] The accuracy of the Doppler technique is approximately ±0.7mm, and the test-retest reliability had an intraclass correlation coefficient of 0.92.[28,33] Cross-correlational analysis entails imaging the excursion with a frame rate approximately 10 frames per second. A region of interest (ROI) is selected and fine structures are marked within the ROI. Pixel gray levels within the region are evaluated in adjacent frames, with pixel shifts corresponding to nerve excursion. To increase the accuracy, frame intervals are increased and analysis is carried out with 1-3 frames between the compared frames. In vivo measurements were found to be reliable measuring movement with less than a 10% error.[32]

It has been hypothesized that excursion rates would be reduced in CTS patients as compared to controls. Hough[28] reported a significantly lower excursion rate; however Erel et al.[29] found no significant difference between CTS patients and controls. This difference in significant findings may be due to the varying methods utilized in the studies. Employing the Doppler technique, Hough measured excursion with the transducer placed longitudinally at the carpal tunnel, with the Doppler sample volume indicator at the location of the lunate-capitate intercarpal joint. From a starting position of either a fully extended or 90˚ flexed elbow, wrist extended 30˚, and fingers fully flexed, excursion was measured as the fingers extended to the maximal allowed amount. Erel measured excursion employing frame-by-frame cross-correlation with the transducer placed 5-15cm proximal from the distal wrist crease. From a starting position with the elbow fully extended and the wrist in neutral, the fingers were extended from a 90˚ flexion to neutral. With both the wrist and the elbow started in an extended position, Hough found a significant reduction of excursion in CTS patients (8.3mm) compared to controls (11.2mm). With the wrist in neutral and the elbow extended, Erel did not find a significant

reduction in median nerve excursion in CTS patients (2.2mm) compared to controls (2.6mm). It is unclear if the positioning differences or the measurement techniques could be responsible for the disagreement between the two studies.[28,29]

Blood is supplied to the median nerve by the radial and ulnar arteries and supply from a persistent medial artery is a normal variant. As the median nerve courses through the carpal tunnel, blood flow is also supplemented by the superficial palmar arch. Injury to the microvessels within the endoneurium results from endured compression and strain, causing ischemia and venous congestion. Edema and inflammation trigger an increased blood flow to the area, further increasing the pressure within and surrounding the carpal tunnel. As inflammation of the nerve ensues, longitudinal images of the median nerve demonstrate a "notched" appearance as the nerve passes under the flexor retinaculum. This abnormal appearance of the median nerve has been employed for the evaluation of CTS. Kele et al.[34] observed 50% of patients had longitudinal compression signs and 39 patients had bulbous nerve swelling. Longitudinal compression had 50% sensitivity and 100% specificity. Wang et al.[35] introduced a semi-quantitative scale to evaluate longitudinal compression sign (LCS), using grades 0-3 to categorize the distortion. A significant difference between subjects and controls ($p < 0.001$) was reported, with sensitivity and specificity rates of 50.0% and 95.8%, respectively.

Hypervascularity at the carpal tunnel inlet is a common presentation in CTS patients. Rahmani et al.[19] evaluated hypervascularity using color Doppler in CTS patients with clinical presentations but normal EDT findings, reporting a significantly higher hypervascularity in CTS patients compared to controls [odds ratio (OR) 5.004]. Only intraneural hypervascularity was considered abnormal, differentiating hypervascularity from normal perineural and prominent median artery vascularity. Mallouhi et al.[22] reported similar findings with a 91% accuracy for

detecting CTS compared to NCS when evaluating hypervascularization with color Doppler sonography. Of the 5 sonographic criteria employed, hypervascularization had the highest sensitivity, positive predictive value, and negative predictive value (95%, 94%, and 75%, respectively).

Improvements in predictive values have been made by employing multivariate sonographic examinations. Rahmani et al.[19] evaluated median nerve CSA, echogenicity, and vascularity in clinically-evidenced CTS patients with normal NCS findings. Using multivariate linear regression analysis, the probability of having clinically-evidenced CTS improved as more sonographic signs were identified. With identification of one sign the probability was 35%, with two it increased to 70%, and with three signs identified the probability increased to 90%. Mallouhi et al.[22] also conducted multivariate examinations to evaluate sonographic predictors of CTS. Of 153 CTS wrists, the presence of both hypervascularity and increased CSA were found in 89% of the wrists compared to 9% having only one of the two signs. Similar improvements were shown by Rempel et al.[17] upon evaluation of specificities of clinical findings. Specificity increased from 76% with the presence of positive physical examinations to 99% with the presence of positive physical examinations, classic or probable symptoms, and night symptoms. Altinok et al.[36] also reported increased sensitivity, specificity, and overall accuracy by evaluating multiple variables. The authors determined the most sensitive variables for diagnosing CTS were swelling ratio (72.5%), CSA at the pisiform level greater than 9mm² (65%), and palmar displacement (62.5%). When two out of the three criteria were present, the sensitivity increased to 95% in identifying moderate CTS and had an overall accuracy of 83.3% for properly classifying normal, mild, and moderate CTS groups. Given that cross-sectional area, longitudinal appearance, excursion, and intraneural vascularity have not been combined as diagnostic

parameters to evaluate CTS, multivariate evaluations may prove valuable as a set of diagnostic criteria for detecting and staging the severity of CTS.

Research Question

Since the use of multiple sonographic measures to diagnose and categorize the severity of CTS has rarely been addressed in the literature, a gap exists. This study was proposed to address this gap with the following research question:

Will the sonographic evaluation of multiple carpal tunnel syndrome indicators, including increased cross-sectional area, abnormal longitudinal appearance, restricted excursion, and intraneural vascularity of the median nerve, aid in the detection and severity categorization of carpal tunnel syndrome?

By investigating this research question, information may be attained that will expand the scope of sonographic evaluation of carpal tunnel syndrome.

Chapter 3: Methods and Analysis

Materials and Methods

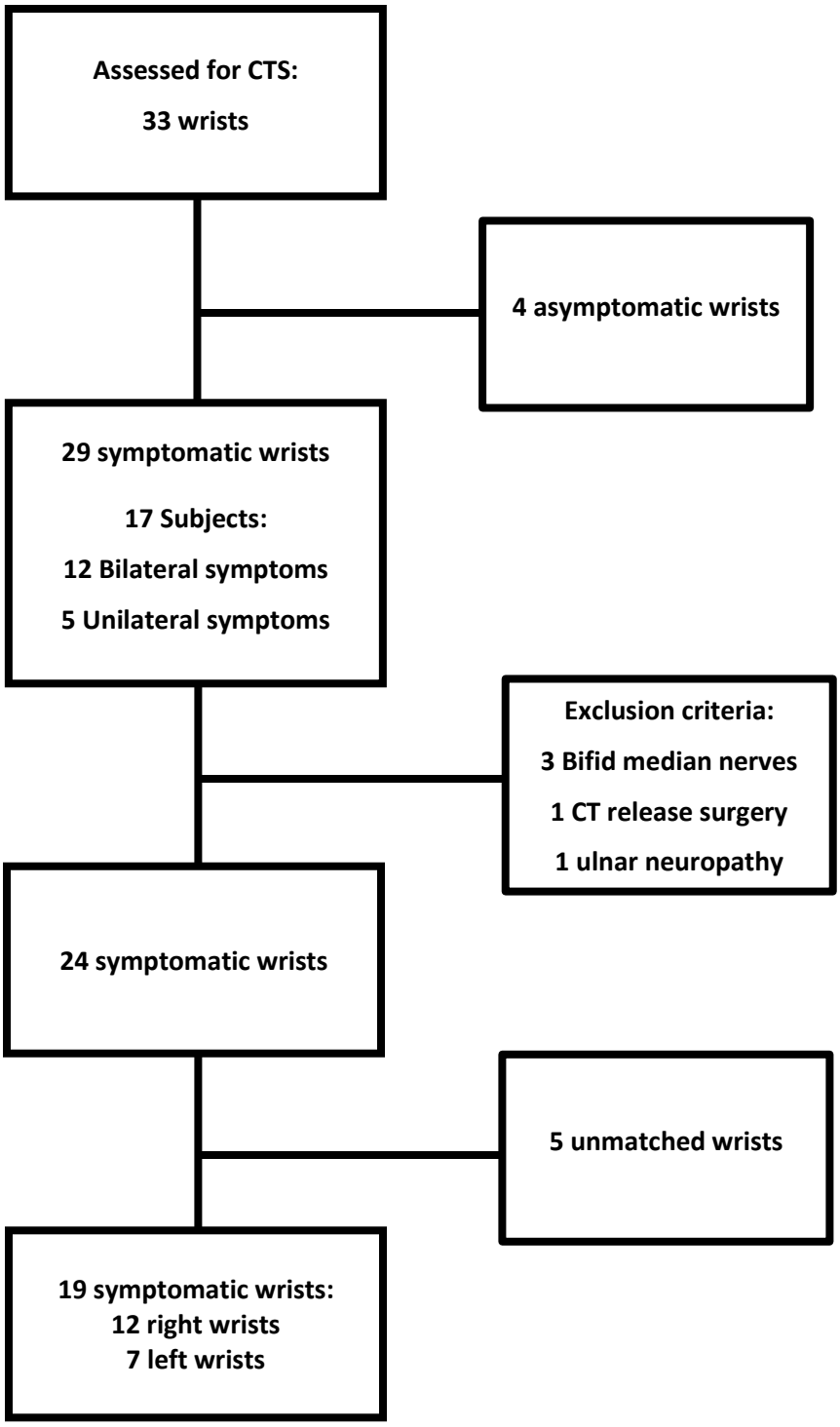
Patients

A retrospective, age and gender matched case-control study was conducted from May 2010 through October 2011. A convenience sample of 38 wrists included 13 symptomatic subjects (19 wrists) and 13 asymptomatic controls (19 wrists). (Figure 3.1) The subjects and controls were matched by examination age within 36 months, gender, and wrist, with the exception of one subject matched to the control's contralateral wrist. Individuals were excluded if a history of uncontrolled diabetes, fractures affecting the carpal tunnel region, previous carpal tunnel release surgery, or current pregnancy was indicated in the medical history. Individuals with bifid median nerves or space occupying mass in the carpal tunnel were also excluded. Symptomatic subjects had sonographic evaluations performed immediately following NCS by a sonographer blinded to the NCS results. Physical examinations and severity surveys were also completed at the time of sonography. Evaluations were performed at The Ohio State University's Cramblett Outpatient Clinic Nerve Conduction Clinic in Columbus, Ohio. The research study was granted approval by The Ohio State University's Biomedical Institutional Review Board.

Nerve Conduction Studies

Nerve conduction studies were considered the gold standard to determine the presence and severity of CTS. Both positive and negative findings were included in the study, and the sonographer was blinded to the NCS results. Carpal tunnel syndrome severity was categorized as normal, mild, moderate, or severe, using guidelines set by The Ohio State University Nerve Conduction Clinic based on standards established by the American Association of

Figure 3.1 Subject Flow Chart



Neuromuscular and Electrodiagnostic Medicine (AANEM). Subjects with sensory values of No Response (NR) were automatically categorized as severe. For comparative purposes, values were assigned to the NCS severity categories as follows: 1-normal, 2-mild, 3-moderate, 4-severe.

Clinical Examination

Individuals were physically examined prior to the sonographic evaluation. Height and weight were attained and the BMI was calculated accordingly. As a precursor to nerve excursion evaluation, maximum extension of the wrist was documented. With the forearm resting medially on a table, test subjects were asked to extend the wrist as far as possible. A goniometer was used to measure the angle between the lateral forearm at the radial stylus process and the index finger to determine the maximum range of motion (ROM) angle. Provocative testing, including Phalen's, Tinel, and Durkan testing, was performed. Testing was considered positive if the individual experienced pain, tingling, or numbness in the hand or wrist within one minute. All individuals completed questionnaires pertaining to symptom and functional status severity. From the completed questionnaire, the absence or presence of classic symptoms and nocturnal symptoms were documented. Classic symptoms were considered present if the individual had symptoms of numbness, tingling, and/or pain in the hand or wrist within two weeks prior to evaluation. Nocturnal symptoms were considered present if pain, numbness, and/or tingling woke the individual more than once in the two weeks prior to evaluation.

Sonographic Evaluation

The median nerve was imaged in transverse and longitudinal planes using high-resolution real-time sonography. Individuals were positioned with the forearm supine, the elbow semi-flexed, and the fingers and the wrist in a neutral position. Evaluations were performed using a

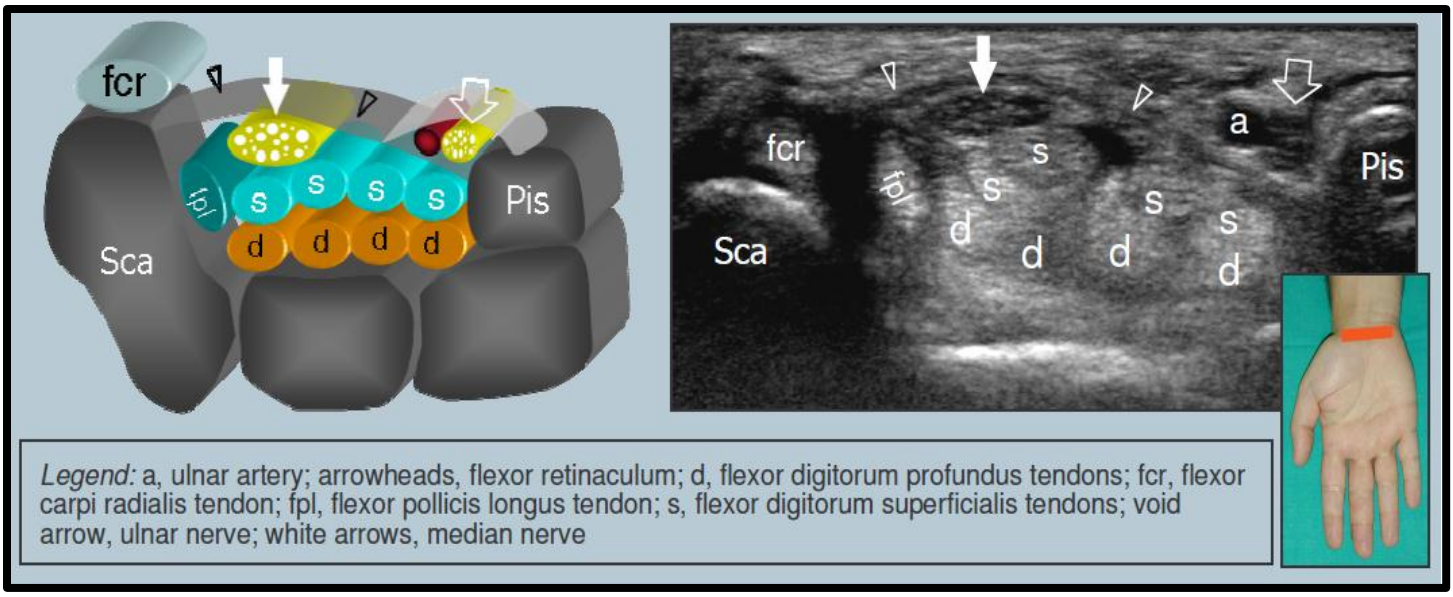


Figure 3.2 Carpal Tunnel Anatomy at the Level of the Pisiform (European Society of Musculoskeletal Radiology. Musculoskeletal Ultrasound Technical Guidelines, http://www.essr.org/html/img/pool/wrist.pdf)

GE Logiq i hand-carried sonographic machine and an 8-12.0 MHz, 43mm linear array transducer (GE Healthcare Clinical Systems, Wauwatosa, Wisconsin). Imaging was performed using the musculoskeletal (MSK) preset, harmonics, and CrossXBeam technology.

The median nerve CSA evaluations were performed in a transverse plane at the carpal tunnel inlet (CSAa) and mid carpal tunnel (CSAb), using the distal radial-ulnar joint and pisiform as anatomical landmarks, respectively. (Figure 3.2) A direct trace method was used to record the CSA, with tracings performed within the epineurium. (Appendix III) Five CSA measurements were attained at both levels; the highest and lowest values were discarded with the remaining three values averaged to determine the mean CSA. Using the CSA means from both locations, the largest CSA (CSAmax) was also recorded. A cut-off value of $10mm^2$ was considered abnormal. Additionally, the CSA area difference was calculated between CSAa and CSAb, with an absolute value difference greater than 3.65 considered abnormal.

Longitudinal appearance, excursion, and intraneural vascularity were evaluated in a longitudinal plane over the carpal tunnel region. (Appendix III) The longitudinal appearance of the median nerve was evaluated for signs of enlargement and compression by the flexor retinaculum. Proximal and distal enlargement and compression were subjectively categorized as present or absent. Cine clips of excursion were obtained at the proximal carpal tunnel inlet using gray-scale sonography. Beginning in the aforementioned starting position, the individual was instructed to slowly extend the wrist from neutral to the maximal extension angle. This maximal amount was assumed to be the same degree of extension as measured with the goniometer prior to sonographic examination. Forward (distal) movement of the median nerve was evaluated using frame-by-frame analysis of the cine clip. Landmarks within the median nerve and carpal tunnel were used to subjectively categorize the excursion as normal or restricted. To evaluate intraneural vascularity within the median nerve, the nerve was imaged using both gray-scale and Doppler sonography. Color Doppler PRF ranged from 0.4-0.6 KHz, depending on the subject. Spectral Doppler was used to evaluate vascularity. Intraneural vascularity was categorized as present or excluded using the following exclusion criteria, developed by Evans et al.[37]: 1) Must demonstrate at least 3 cardiac cycles in the sample, 2) must have the spectral Doppler gate positioned within the median nerve, 3) must have more than pulsatility in the spectral tracing, 4) must have an optimized gray scale image, 5) must have a signal greater than noise ratio, and 6) must have a color pixel within the spectral Doppler gate.

Sonographic Severity Categorization

A scoring matrix was developed incorporating multiple sonographic and clinical CTS indicators to categorize the CTS severity. Carpal tunnel syndrome severities were categorized as

Sonographic and Clinical Indicators
CSAmax > 10mm²
CSAmax > 13mm²
CSAmax > 15mm²
Longitudinal Compression
Proximal Enlargement
Restricted Excursion
Positive Provocative Test
Classic Symptoms Present
Nocturnal Symptoms Present

Table 3.1 CTS Indicators for US Severity

CATEGORY	SEVERITY	POSITIVE MARKERS
1	Normal	0-1
2	Mild	2-4
3	Moderate	5-7
4	Severe	8-9

Table 3.2 US Severity Categories

normal, mild, moderate, and severe. Categories were assigned the same values as the NCS categories for comparative purposes (normal-1, mild-2, moderate-3, severe-4). Subjects and controls were both scored and categorized. Categories were assigned according to the number of positive CTS indicators (normal=0-1, mild=2-4, moderate=5-7, severe=8-9). (Table 3.1, 3.2)

Statistical Analysis

Mean values, ranges, and standard deviations (SD) were calculated for age, BMI, CSAa, CSAb, CSAmax, CSA area difference, and ROM. Data entry and statistical analysis was performed using Microsoft Excel 2010 and SPSS Version 19 for Windows (Chicago, IL). Binomial statistics were coded using 1 for normal (negative), 2 for abnormal (positive), and 0 for excluded or missing values. Student *t* tests (two-tailed, assuming unequal variances) were performed to compare independent variables between subject and control groups. Spearman correlations and Student *t* tests (two-tailed, assuming equal variances) were performed to determine the association and statistical significance between subject independent variables (age,

BMI, CSAa, CSAb, CSAmax, CSA area difference, ROM) and NCS severity. Chi-square analysis was used to calculate the agreement between sonographic (US) and NCS severity categories. P values > 0.05 were considered statistically significant. Strength of association was considered weak (< 0.3), moderate (0.3-0.7), or high (> 0.7).[38]

Chapter 4: Results

Demographics

The subject cohort consisted of 13 individuals (9 female, 69.23%). Symptoms were bilateral in 6 subjects and unilateral in 7, for a total of 19 wrists. Subject age ranged from 23-62 years (mean age, 43.85 ± 10.71 years) at the time of the examination. The control cohort consisted of 13 individuals (9 female, 69.23%) and 19 wrists. Control age ranged from 23-61 years (mean age, 43.84 ± 10.02 years) at the time of the examination. Mean subject BMI (30.39 ± 9.55) and control BMI (27.72 ± 5.09) were not significantly different ($p>0.05$). (Table 4.1)

Subjects versus Controls

Mean CSA measurements were significantly increased in subjects as compared to control CSA values (Table 4.1, Figure 4.1). The mean CSAa (13.00 ± 3.91mm^2) and CSAb (12.98 ± 3.24mm^2) in subjects was statistically significant compared to CSAa (9.52 ± 3.25mm^2) and CSAb (8.86 ± 2.89mm^2) in controls ($p<0.01$ and $p<0.0001$, respectively). Additionally,

Variable	Subject	Control	p=
Age, years	43.85 ± 10.71	43.46 ± 10.95	0.93
% Female	69.23%	69.23%	
BMI	30.39 ± 9.55	27.72 ± 5.09	0.38
CSAa, mm^2	13.00 ± 3.91	9.52 ± 3.25	< 0.01
CSAb, mm^2	12.98 ± 3.24	8.86 ± 2.89	< 0.001
CSAmax, mm^2	14.76 ± 3.86	10.36 ± 3.35	<0.001
CSA Area Difference, mm^2	3.53 ± 2.78	2.35 ± 1.95	0.14

Table 4.1 Subject and Control Variable Means ± SD and Significance, reported as mean ± SD

CSAmax was significantly increased in subjects (14.76 ± 3.86) compared to controls (10.36 ± 3.35mm²) ($p<0.001$). Using a cut-off value of 10mm^2, 84.21% of subjects had a CSAmax over the cut-off value compared to 52.63% of controls. The difference between subjects and controls increased as the CSAmax increased to more than 15mm^2, 47.37% of subjects compared to 5.26% of controls. The mean CSA area difference was not found to be significantly different between the two groups ($p>0.05$).

While none of the controls presented with abnormal longitudinal median nerve appearance, 52.63% of subjects had at least one abnormal presentation. Of the three evaluated, compression was the most frequent (52.63%), followed by proximal enlargement (42.11%) and distal enlargement (10.53%). Controls had a greater percentage of intraneural vascularity compared to subjects, 63.16% and 52.63%, respectively. Restricted excursion was observed in

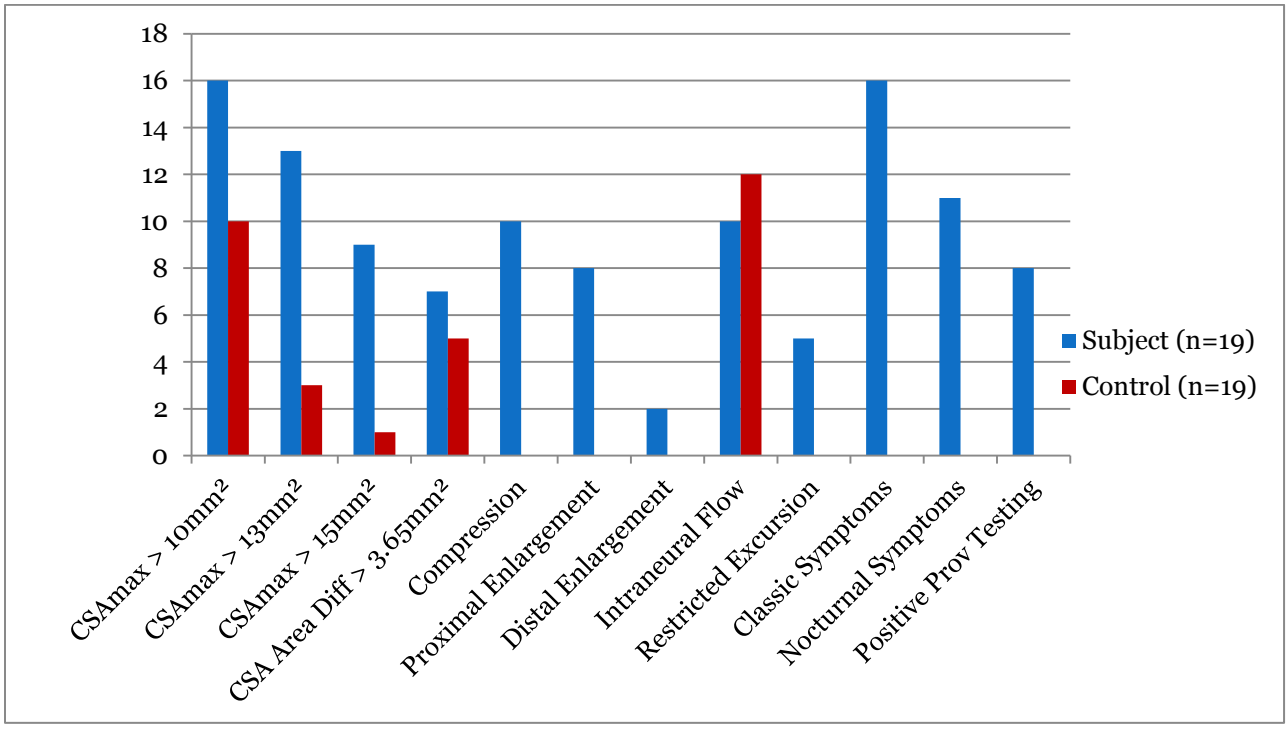


Figure 4.1 Variable Frequencies in Subject and Control Groups

26.32% of subjects and was only observed in subjects with a CSAmax greater than 15mm^2. Range of motion (ROM) and excursion were not evaluated in the control cohort. Clinical evaluation included provocative testing and symptom presentations. Provocative testing was normal in all controls and none experienced classic or nocturnal symptoms. By comparison, 42.11% of subjects had at least one positive provocative test, 84.21% experienced classic symptoms, and 57.89% reported nocturnal symptoms. (Appendix VII)

Subjects versus NCS Severity

At the wrist level analysis, mean subject age and BMI were slightly higher than the individual level due to the increased sample (13 individuals compared to 19 symptomatic wrists), with a mean subject age of 43.89 ± 9.68 and BMI of 32.03 ± 10.08. Increases in subject BMI, CSAa, CSAb, and CSAmax had statistically significant moderate associations with increasing severity based on NCS (Table 4.2). Age, CSA area difference, and ROM had weak associations with increasing severity, and of the variables CSA area difference was not significant ($p>0.05$).

VARIABLE	MEAN (±SD)	p=	r=
Age, years	43.89 (9.68)	<0.01	0.24
BMI	32.03 (10.08)	<0.01	0.60
CSAa, mm^2	13.00 (3.91)	<0.01	0.36
CSAb, mm^2	12.98 (3.24)	<0.01	0.53
CSAmax, mm^2	14.76 (3.86)	<0.01	0.49
CSA Area Difference (CSAb-CSAa), mm^2	3.53 (2.78)	0.25	0.24
ROM, degrees	48.53 (14.94)	<0.01	-0.20

Table 4.2 Mean, SD, and Significance of Subject Variables (wrist level) Compared to NCS Severity

Variable	Normal (n=2)	Mild (n=7)	Moderate (n=4)	Severe (n=6)
CSAmax > 10mm^2	50.00%	85.71%	75.00%	100.0%
CSAmax > 13mm^2	50.00	42.86	75.00	83.33
CSAmax > 15mm^2	50.00	14.29	50.00	83.33
Compression	50.00	42.86	50.00	66.67
Proximal Enlargement	50.00	14.29	50.00	66.67
Restricted Excursion	0.00	0.00	25.00	66.67
Provocative Testing	Excluded	14.29	75.00	66.67
Classic Symptoms	50.00	100.0	100.0	66.67
Nocturnal Symptoms	50.00	28.57	100.0	66.67

Table 4.3 Subject Variable Percentages by NCS Severity

Based on NCS, severity categorization resulted in 2 normal, 7 mild, 4 moderate, and 6 severe CTS subjects. (Figure 4.2) Subject BMI increased with severity, increasing from 21.55 in normal subjects to 39.62 in severe subjects, as did CSAb, increasing from 9.92 ± 0.09mm² in normal subjects to 14.94 ± 2.85mm² in severe subjects. (Table 4.4) Severe CTS subjects had the highest percentage of sonographic variables, and the majority of severe subjects had a CSAmax greater than 15mm^2 (83.33%). Restricted excursion was only observed in moderate and severe subjects. (Table 4.3)

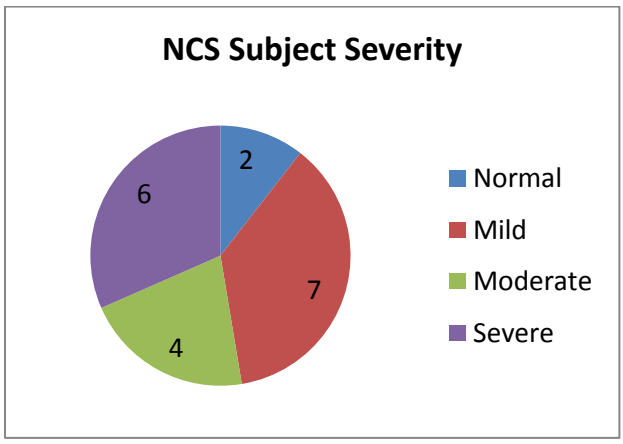


Figure 4.2 Subject Severity Based on NCS

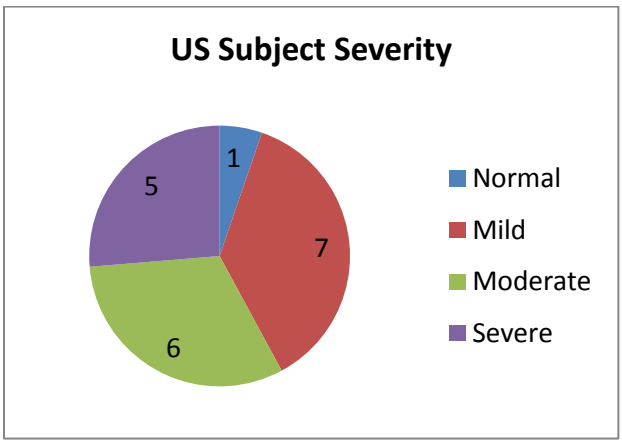


Figure 4.3 Subject Severity Based on US Scoring

Severity	n=	BMI	CSAa	CSAb	CSAmax
Normal					
NCS	2	21.55 ± 4.17	12.60 ± 7.90	9.92 ± 0.09	14.02 ± 5.89
US	1	29.50 ± 0	11.36 ± 0	11.69 ± 0	11.69 ± 0
Mild					
NCS	7	28.37 ± 2.92	11.45 ± 1.82	11.80 ± 2.74	12.49 ± 2.40
US	7	27.04 ± 4.35	10.67 ± 2.41	11.38 ± 3.02	12.07 ± 2.82
Moderate					
NCS	4	32.30 ± 8.29	12.48 ± 3.66	13.66 ± 4.09	14.93 ± 4.34
US	6	28.18 ± 4.88	12.24 ± 3.21	13.67 ± 3.64	15.04 ± 3.51
Severe					
NCS	6	39.62 ± 13.39	15.29 ± 4.55	14.94 ± 2.85	17.54 ± 3.42
US	5	44.14 ± 12.20	17.49 ± 3.32	14.66 ± 2.83	18.80 ± 2.01

Table 4.4 BMI and CSA Measurements by NCS and US Severity, CSA reported as mean ± SD in mm²

Sonographic Severity Categorization

A scoring matrix incorporating sonographic and clinical CTS indicators was used to categorize severity. (Table 3.1, 3.2) Based on the scoring, US severity categorization resulted in 1 normal, 7 mild, 6 moderate, and 5 severe CTS subjects. (Figure 4.3) Mean CSAmax increased with severity, increasing from 11.69mm² in normal subjects to 18.80 ± 2.01mm² in severe CTS subjects. Mean BMI, CSAa, and CSAb also increased with severity when normal values were excluded.

Sonographic Severity versus NCS Severity

An overall agreement of 63.16% was observed between US and NCS severities, and the level of agreement was determined to be statistically significant using chi-square analysis

	NCS Normal	NCS Mild	NCS Moderate	NCS Severe	Total
All Subjects (n=19)	0/2 (0.00%)	5/7 (71.43%)	3/4 (75.00%)	4/6 (66.67%)	12/19 (63.16%)
Less subjects with excluded variables (n=14)	Excluded	5/6 (83.33%)	3/4 (75.00%)	4/4 (100.0%)	12/14 (85.71%)

Table 4.5 Subject US and NCS Severity Category Percentage Agreement

($p<0.05$). The highest agreements were observed in mild (71.43%) and moderate CTS subjects (75.00%). Normal subject severity according to US did not agree with NCS severity, with US scoring categorizing one subject as mild and one as moderate. The majority of mild subject severity agreed (5/7) and both subjects not in agreement had an US severity of moderate. The majority of moderate subjects were also in agreement (3/4), with one scored as severe by US severity. Although severe CTS subject severity agreed between NCS and US in 66.67%, this category had the most disagreement between categorization. The two subjects not in agreement were scored as one normal and one mild by US severity. (Appendix X) Five of the seven subjects with differing NCS and US severities had missing values, including excursion, provocative testing, and symptom presentations. (Appendix X) Agreement increased between US and NCS severity when subjects with missing values were excluded, reaching an overall agreement of 85.71%. (Table 4.5)

Chapter 5: Discussion

Historically, clinical evaluation and electrodiagnostic testing have been used to detect and stage the severity of CTS. Over the past two decades, the use of ultrasound to evaluate CTS has made many advances but has yet to surpass NCS, especially in the staging of CTS severity. The purpose of this study was to explore the use of multiple CTS indicators, blending both qualitative and quantitative variables, as a means for detecting and staging the severity of CTS.

A multitude of variables were evaluated to assess the difference between subjects and controls as well as the difference between NCS severity categories. Cross-sectional area was found to be useful in evaluating CTS, with significant differences observed between subjects and controls. This included the CSA at the proximal and mid carpal tunnel as well as the largest CSA measure ($p<0.01$). A moderately significant positive correlation was also found between these measures and NCS severity. Of the studies evaluated in Roll's systematic review, the CSA at the level of the pisiform was the most commonly used and the most accurate measure.[25] Similarly, the present study concluded the CSA at the level of the pisiform (CSAb) had the strongest correlation with CTS severity. Although this mid tunnel measurement may be the most indicative, other CSA measures may be necessary for a thorough evaluation. As explained by Roll,[25] the carpal tunnel may not accommodate for swelling within the tunnel and swelling may occur just proximal to the tunnel instead. Ziswiler et al.[39] identified the largest CSA within the carpal tunnel region, reporting high concordance between the largest CSA measurement and NCS. The present study also used the largest CSA measurement, although this was determined as the largest of the proximal and mid carpal tunnel CSA means. Employing the largest CSA measure aided in the proper assessment of subjects by US; three out of four subjects with pisiform-level CSA measurements less than $10mm^2$ and proximal tunnel CSA measurements

greater than 10mm^2 were correctly staged by US with mild CTS. Of the CSA parameters evaluated, CSA area difference was not found to be helpful in evaluating CTS. Unlike Akcar's findings,[21] a lack of significance was observed between subjects and controls and with increasing NCS severity in the current study.

Longitudinal appearance of the median nerve is seldom reported in the literature. As previously mentioned, the carpal tunnel may not accommodate an inflamed median nerve and a notched or hourglass appearance may be observed when the nerve is imaged longitudinally. Studies have reported longitudinal compression sign (LCS) sensitivities ranging from 50-91.7% and specificities ranging from 62.5-100%, concluding that LCS is a useful sonographic variable for evaluating CTS.[34,35] In concordance with these findings, over half of the subjects (52.63%) had observed compression which did not compare to the controls (0%). Similarly, proximal median nerve enlargement was observed in 42% of subjects and no controls. Kele also reported enlargement of the median nerve, describing a "bulbous nerve swelling" observed in 39 of the 55 subjects with an identified compression sign.[34] Distal enlargement was not found to be a beneficial parameter as it was only observed in two subjects. The highest percentages of compression and proximal enlargement were observed in subjects with severe CTS compared to other severity categories.

Evaluation of intraneural vascularity has received more attention over the last decade in the evaluation of CTS. Akcar evaluated the number of vessels observed in the median nerve within carpal tunnel region using power Doppler, reporting vessels in 50% of subjects and none of the controls. The authors proposed the quantification of vessels may be beneficial for CTS severity grading.[21] Mallouhi concluded vascularity contributed more than gray-scale parameters in detecting CTS as compared to NCS, reporting the highest levels of sensitivity, PPV, NPV, and

overall accuracy rates were achieved with hypervascularity.[22] Surprisingly, the current study observed intraneural flow in more asymptomatic controls than in symptomatic subjects (63% versus 53%, respectively). However, the results may be concordant with reported findings by Evans.[37] The authors observed an inverse relationship between intraneural vascular flow and increasing severity, with peak systolic values of 3.75cm/s in symptomatic subjects and 4.26cm/s in asymptomatic controls. It was proposed that as progressive and chronic CTS develops, a decrease in tissue perfusion occurs, with a resultant decline in peak systole. Additional research conducted by Evans et al.[40] evaluated intraneural flow within different regions of the carpal tunnel using spectral Doppler analysis in symptomatic subjects and asymptomatic controls. There were no statistical differences observed between subject and control waveform frequencies. Vascularity within the median nerve was also compared to the number of positive provocative tests. An increase in positive provocative tests corresponded to an increase in mid-tunnel peak systolic velocities (PSV) and a decrease in proximal tunnel PSV, however the authors concluded there was not a clear directional relationship between provocative testing and PSV (R^2=0.01). Although strict criteria were used for determining the presence of flow in the present study, this parameter may be better evaluated with a larger sample size to determine the clinical significance of intraneural flow.

Restricted excursion is another area that may benefit from future research utilizing larger sample sizes. Hough reported a reduced excursion in 57.9% of subjects and 8.1% of subjects, also reporting a higher prevalence in the dominant arm and in those with positive provocative testing.[28] Although restricted excursion was only observed in 26.32% of subjects in the present study, it was only identified in moderate and of severe CTS subjects (25% and 66.67%, respectively). Also of interest, all subjects with restricted excursion had a CSAmax greater than

$15mm^2$, compression and proximal enlargement signs, two or more positive provocative tests, and the presence of both classic and nocturnal symptoms.(Appendix X) Because this was a retrospective study, the previously established protocol for imaging controls did not include excursion evaluations. Comparative information between subjects and controls is not available; however the findings within the subject cohort are promising and may warrant additional exploration.

Although the use of qualitative parameters in addition to quantitative parameters is not a new approach, to the author's knowledge the combination of variables used in this study is unique to current CTS research. Qualitative parameters used to evaluate CTS include longitudinal compression sign and echogenicity of the median nerve, typically in conjunction with quantitative parameters, CSA being the most common.[19,22,34,35] In addition to qualitative assessments, Karadag et al.[41] emphasized the importance of evaluating CTS from different perspectives. Karadag[41] and Padua[20] both explored the relationships between CSA and clinical presentations of CTS, including functional and symptom status questionnaires and provocative testing, in addition to NCS. Both authors reported significant findings between ultrasound and clinical presentations, as well as between ultrasound and NCS. The use of multidimensional assessments has also been shown to increase the predictive value of sonographic detection of CTS.[17,19,21,22,34-36] Kele reported the best accuracy was received when using both qualitative and quantitative evaluations.[34] Altinok reported increased accuracy in correctly classifying CTS severity when multiple variables were used.[36] Similarly, Rempel evaluated the use of clinical parameters to predict the likelihood of CTS, reporting the greatest predictive value when combining the presence of classic/probable symptoms, nocturnal symptoms, and abnormal physical examination (positive provocative testing).[17]

Severity staging is especially important for the management of patients, including the decision to treat patients conservatively or proceed with surgical interventions. The usefulness of sonography to evaluate CTS will not surpass NCS until a reliable method has been established to accurately stage CTS severity. Few studies have been successful at categorizing CTS severity in agreement with NCS. El Miedany[24] and Karadag[41] both observed significant differences between severity groups (normal, mild, moderate, severe) using tiered CSA grading recommended by El Miedany, also reporting significant correlations between abnormal electrodiagnostic testing and ultrasound grades. Kang et al.[42] revealed significant differences between controls and mild, moderate, and severe CTS subjects when using a wrist-to-forearm median nerve area ratio (WFR). When using the CSA at the wrist (CSA-W), a significant difference was observed between controls and subject severity groups but this parameter did not identify a significant difference between mild and moderate CTS subjects. While studies seem to easily differentiate between normal and abnormal subjects, research has often failed to determine significant differences between severity groups, especially in differentiating mild CTS from other severities.[42-45]

Based on the current research, a multifaceted approach was used in this study, employing both quantitative and qualitative parameters, evaluating the most prevalent sonographic measures in conjunction with clinical presentations. The scoring matrix employed for US severity scoring is a fusion of parameters inspired by research conducted by authors including El Miedany, Kele, Hough, and Rempel. Using tiered CSA levels, qualitative longitudinal appearance and excursion evaluations, and clinical presentations, a semi-quantitative scale has been introduced with the particular goal of aiding severity staging. Although this pilot study has a small sample of symptomatic subjects (n=19) evaluated by NCS and sonography, significant agreement was

observed between NCS and US severity ($p<0.05$). Ultrasound severity scoring correctly classified 71% of mild, 75% of moderate, and 67% of severe CTS subjects according to NCS severity.

Although the current scoring matrix correctly identified 84% of the controls as normal (16% graded as mild), the symptomatic subjects diagnosed as normal by NCS had the most disagreement between NCS and US. Of the two normal subjects, one was graded as mild and one was graded as moderate. The first subject, graded as mild, did not have any positive ultrasound indicators or positive provocative testing, but was scored as mild based on the presence of classic and nocturnal symptoms. The normal subject graded as moderate was even more perplexing, with a CSAmax of $18mm^2$, compression, and proximal enlargement.(Appendix XI)

It has been proposed by other authors that false-positive ultrasound findings may in fact be attributed to false-negative NCS findings.[19,46] Similarly, authors have concluded that subjects with typical CTS clinical presentations and normal evaluations, either by NCS or US, should not be precluded from a diagnosis of CTS and follow-up testing may be necessary.[19,24,37,43,44,46] Mondelli[43] reported 23.5% of subjects clinically diagnosed with mild CTS had negative NCS and US tests. Similarly, Moran[44] reported 28.6% of subjects with suspicion of CTS had negative NCS results. In a study evaluating clinically diagnosed CTS subjects with normal NCS, Rahmani[19] calculated a probability of CTS ranging from approximately 35-90% depending on the number of positive ultrasound parameters. Wong[46] reported a false-positive US rate of 11-15%, a rate comparable to generally accepted NCS false-negative rates. The authors suggested these subjects may be better classified as false-negative NCS result rather than a false-positive upon US.

Several authors have offered possible explanations for the discordance between CTS symptoms and US or NCS evaluations.[37,43,44,46] In the early stages of CTS, intermittent ischemia caused by repetitive strain can present as paresthesia in affected individuals, occurring prior to demyelination of the nerve. As ischemia ensues, damaged nerve-blood barriers allow capillary leakage into the epineurium, leading to edema. Increased cross-sectional area of the median nerve will not occur until after edema triggers the inflammation process, also triggering hypervascularity within the area. If NCS is performed prior to demyelination, the findings will likely be normal. Similarly, if US is performed before edema has effectively initiated the inflammation process, ultrasound parameters will also likely be normal. It is also possible that acute inflammation can increase CSA and vascularity prior to demyelination, potentially creating an abnormal US examination and a normal NCS examination. Considering the mechanisms of acute inflammation, the subject staged as normal by NCS with a CSA greater than $18mm^2$ may represent an NCS false-negative, rather than an US false-positive.

The use of sonography as a first-line diagnostic test has been proposed within the literature.[15,18,24,39,44,46,47] Generally accepted advantages of sonography include wide availability, noninvasive, well-tolerated by patients, and cost-effective. In a random post-examination survey conducted by Visser et al.,[47] 60% of patients preferred sonography compared to only 5% reporting a slight preference for EMG. Of the proponents for first-line sonography evaluations, most concur that electrodiagnostic testing and ultrasound would be complementary, as electrodiagnostic testing would be beneficial for the evaluation of symptomatic subjects with normal US findings.[18,39,43,44,47] Research has shown increasing the use of sonography for CTS evaluation can provide significant reductions in cost and time.[15,39,46] In Hong Kong, a 30 minute electrodiagnostic evaluation costs $320 (U.S. dollars), compared to a $60 (U.S. dollar) 15 minute

sonographic examination.[46] Ziswiler[39] concluded the use of sonography for the initial evaluation of patients with CTS symptoms could cut the use of EDX in half, resulting in a cost reduction of $108 (U.S. dollars) per symptomatic wrist. While the benefits of sonography are encouraging, the progress to sonography as a first-line examination for CTS would benefit from a universally accepted protocol and method for staging the severity of CTS.

Chapter 6: Conclusion

Although the results are promising and may be of value in future research, there are several inherent limitations. The most notable of the limitations is the small sample size. Based on a combined subject and control sample size of 38, as well as a smaller cohort of 19 symptomatic subjects undergoing both NCS and US testing, the results obtained in this pilot study cannot be generalized to larger populations. Additionally, because this was a convenience sample, recruiting volunteer subjects appearing for NCS evaluation and volunteer controls responding to flyers, the generalizability of the results is further reduced. Prospective studies with increased recruitment are necessary to determine the clinical significance of the multidimensional evaluation and scoring system proposed in this pilot study.

Missing parameter values was another significant limitation in this pilot study, potentially causing an under-estimation of parameter frequency and US severity-scoring. Five symptomatic wrists were missing data, specifically excursion (1), provocative testing (4), and presence of classic and nocturnal symptoms (3). Pertaining to the missing symptom information, although the nerve conduction testing was order for symptoms consistent with CTS, a completed functional and symptom status questionnaire was not completed and these subjects also had missing provocative testing. The individuals were mentally handicapped, with a general lack of understanding and inability to provide information pertaining to their symptoms. Although the missing data was a disadvantage, it should be noted that this is certainly a situation that may be encountered in larger studies. Specific populations and settings may be unable to provide information relevant to their care, including cognitively challenged or geriatric populations.

Another limitation of this pilot study is the lack of comparison between subject and control electrodiagnostic testing. Controls did not undergo NCS evaluation due to a lack of funding for such a venture. This would have been especially useful for asymptomatic controls presenting with abnormal US findings presentations. As previously stated, this was a convenience sample relying on volunteer controls from an academic setting. Three asymptomatic controls had a CSA larger than $13mm^2$, one of which had a CSA larger than $15mm^2$. These subjects were all staged as mild CTS by US. Comparing the US staging, based on the enlarged CSA values, to NCS findings may have provided valuable information. In addition to increased sample sizes, future research would benefit from the inclusion of electrodiagnostic testing on both symptomatic subjects and asymptomatic controls to further evaluate the accuracy of the US scoring matrix.

Continued focus on excursion in future research is also suggested. This pilot study was a retrospective case-control study, and control data was attained from an established database of examinations. The original protocol did not include the evaluation of excursion, resulting in a lack of information on excursion in healthy, asymptomatic controls. Although restricted excursion was only observed in subjects with NCS findings diagnosing moderate or severe CTS, there is a need for comparative studies between subjects and controls. Future studies replicating the combination of parameters and scoring system should include the evaluation of median nerve excursion in all individuals.

The qualitative evaluation of excursion did provide results worthy of future exploration; however this parameter was intended to be a quantitative variable, reporting excursion rates in millimeters. Originally, frame-by-frame analysis was proposed to evaluate distal movement of the median nerve upon active wrist extension. Audio video interleave (AVI) files were uploaded

into a video processing software program, VirtualDub (version 1.9.11), used to break down the files into individual frames. Using Microsoft Paint, the individual frames were marked with colored dots at the carpal tunnel inlet on every fifth frame to create a point of reference. Longitudinal segments were then color highlighted on every other frame. The individual frames were then reassembled and evaluated. It was hypothesized that the observed pixel shifts would allow for the angle of excursion.and forward motion to be evaluated, converting the movement into millimeters for a quantifiable measurement. After repeated attempts, this method of analysis was unsuccessful, and the current qualitative assessment of excursion was adopted. Although quantitative evaluations of excursion were not successful in this pilot study, future research should explore existing or new techniques to accurately measure excursion rates. Confirmatory studies may indicate restricted excursion is a useful parameter to evaluate and stage the severity of CTS.

In conclusion, significant agreement between US and NCS severities was achieved using a multidimensional evaluation of sonographic and clinical parameters. Additional research using the qualitative and quantitative evaluations employed in the present study may be valuable for guiding clinical practice, and larger replicated studies are encouraged. The practicality of the proposed system should be evaluated as this approach may provide clinicians with a holistic approach for the initial diagnosis and severity staging of CTS.

Appendices

List of Abbreviations

AANEM	American Association of Neuromuscular and Electrodiagnostic Medicine
ARM	Right (R) or left (L) wrist
AVI	Audio video interleave
BMI	Body mass index
CLASS SYMP	Classic symptoms
COMP	Compression
CON	Control
CON ID	Control identification number
CSA	Cross-sectional area
CSAa	Cross-sectional area at the carpal tunnel inlet, at the level of the radial-ulnar joint
CSAb	Cross-sectional area at mid-tunnel, at the level of the pisiform
CSAmax	Largest of the inlet and mid-tunnel cross-sectional area measurement
CSA AREA DIFF	Cross-sectional area difference (CSAb-CSAa)
CT	Computed tomography
CTS	Carpal tunnel syndrome
DIST ENLG	Distal enlargement
EDX	Electrodiagnostic study
EMG	Electromyography
EXCURS	Excursion
FSS	Functional status survey
IN FLOW	Intraneural vascular flow
LCS	Longitudinal compression sign
MATCH	Matched subject or control identification number
MRI	Magnetic resonance imaging
MSK	Musculoskeletal
NCS	Nerve conduction study
NCS CAT	Nerve conduction study severity category
NOCT SYMP	Nocturnal symptoms
NPV	Negative predictive value
NR	No response
PPV	Positive predictive value
PROV TEST	Provocative testing
PRX ENLG	Proximal enlargement
ROI	Region of interest
ROM	Range of motion
SCORE	Number of positive parameters
SD	Standard deviations
SSS	Symptom severity survey
SUB	Subject
SUB ID	Subject identification number
US	Ultrasound
US CAT	Ultrasound severity category
VTI	Velocity time integrals
WFR	Wrist-to-forearm median nerve area ratio

DATA WORKSHEET

Subject: _____ Hand: R L Exclusion: _____

DOB: _____ Symptomatic: Y N

Exam date: _____ Gender: M F Dominant Hand: R L

BMI: _____

Cross-Sectional Analysis (mm²)

	CSAa	CSAb
1		
2		
3		
4		
5		
Trimmed Average		
Frame Number		

Longitudinal Appearance

Compression	Present	Absent	Excluded
Enlargement:			
Distal	Present	Absent	Excluded
Proximal	Present	Absent	Excluded

Intraneural Flow Present Excluded

Waveforms: Total _____

Present _____ Excluded _____

Excursion Normal Restricted Excluded

ROM: _____

Provocative Testing

Phalen's	+	-
Tinel's	+	-
Durkin's	+	-

NCS Diagnosis Normal Mild Moderate Severe

SCORING MATRIX

ID: _____

Sonographic Evaluation

CSA:

Largest CSA >10mm^2	1
Largest CSA >13mm^2	1
Largest CSA >15mm^2	1

Longitudinal Appearance:

Compression	1
Proximal Swelling	1
Restricted Excursion	1

Total Positive US Indicators: _____

Clinical Examination and Symptoms

Positive provocative test	1
Classic symptoms present	1
Nocturnal symptoms present	1

Total Positive Clinical Indicators: _____

Total Positive Indicators: _____

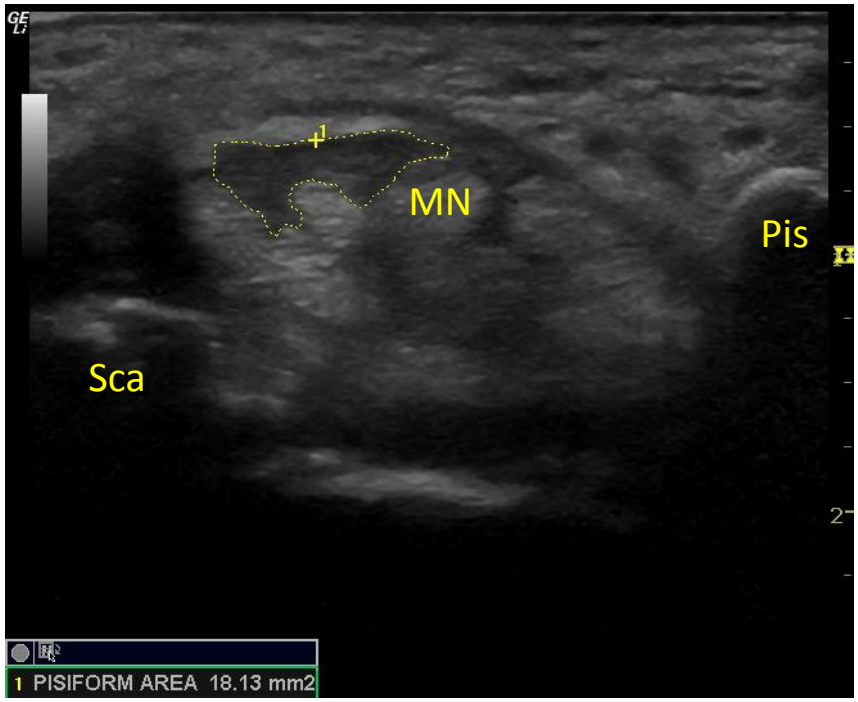
CTS Severity

Normal	0-1	_____
Mild	2-4	_____
Moderate	5-7	_____
Severe	8-9	_____

NCS Category: _____

Sonographic Images: Cross-Sectional Area of the Median Nerve

Subject



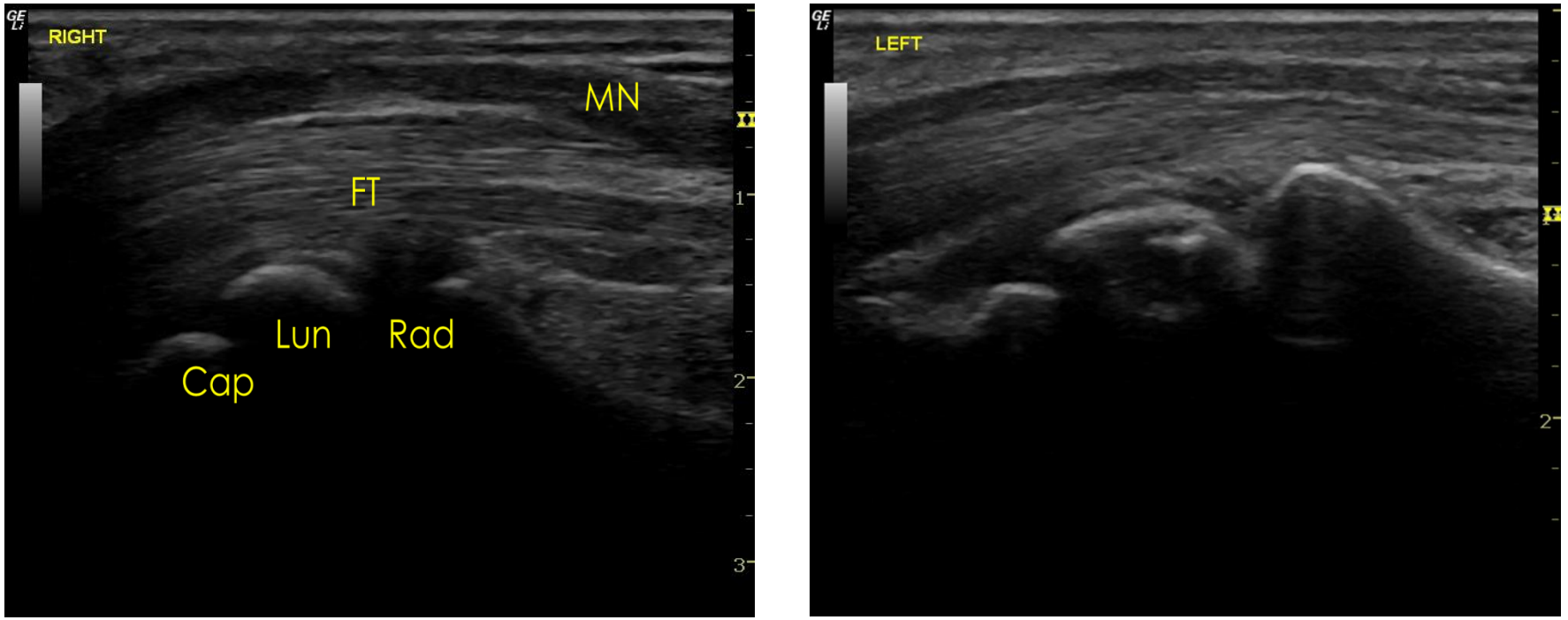
Control

Cross-sectional area of the median nerve at the level of the pisiform (CSAb), calculated using a direct trace method. CSA greater than 10mm^2 considered abnormal.

MN-median nerve, Sca-scaphoid, Pis-pisiform

Sonographic Images: Longitudinal Appearance of the Median Nerve

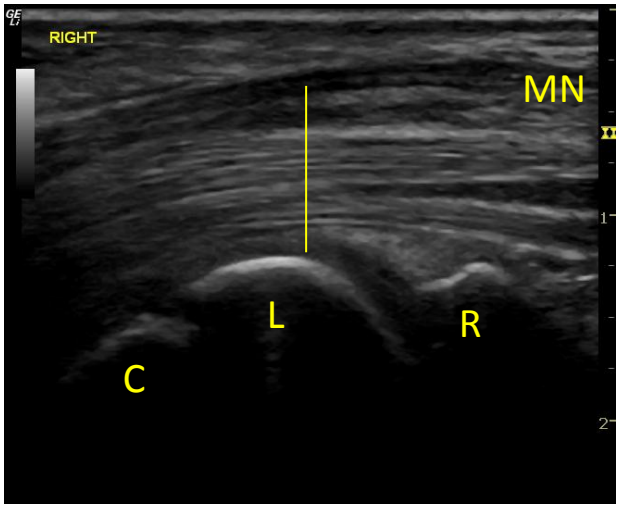
Subject **Control**



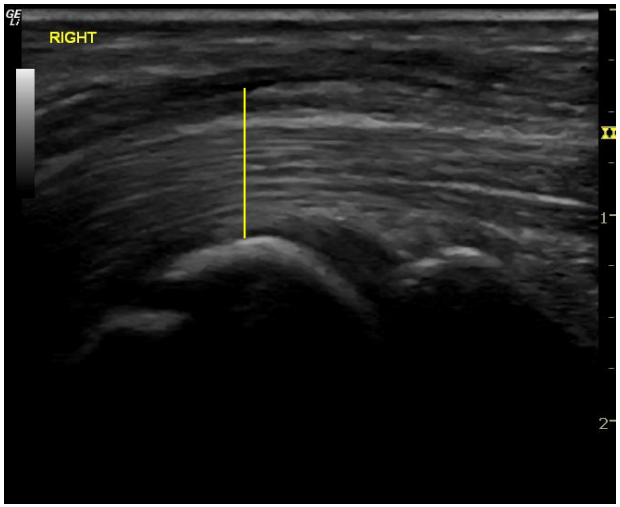
Longitudinal images used to subjectively evaluate enlargement and compression of the median nerve in the carpal tunnel region.

MN-median nerve, FT-flexor tendons, Rad-radius, Lun-lunate, Cap-capitate

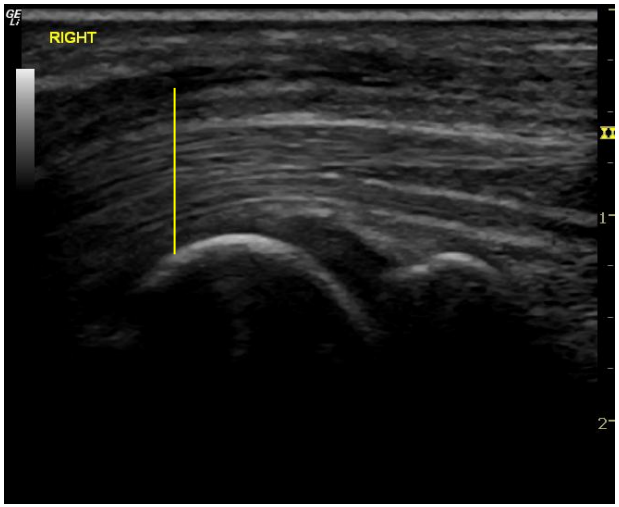
Sonographic Images: Excursion of the Median Nerve



43.121



64.121



115.121

Individual frames (frame number located below image) from cine clip of median nerve excursion upon active wrist extension. Intraneural reference point and anatomical landmarks used to subjectively classify excursion as normal or restricted.

MN-median nerve, R-radius, L-lunate, C-capitate

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